The role of sonoelastography in acute, subacute and chronic thyroiditis: a novel application of the method

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Abstract

Objective: Reports on sonoelastography, which provide an objective estimation of tissue elasticity, are scarce in terms of thyroiditis. The aim of this study was to prospectively assess the applicability of sonoelastography in different types of thyroiditis.

Design: The study assessed and compared the thyroid tissue stiffness in patients with acute thyroiditis (AT), subacute thyroiditis (SAT), and chronic autoimmune thyroiditis (CAT) with healthy control subjects (CS), followed up for 10 weeks.

Methods: The study group consisted of two patients with AT, 18 patients with SAT, 18 patients with CAT, and 40 CS matched for age and gender. Sonoelastography was performed at baseline, at a 4-week follow-up during treatment, and at 10 weeks following diagnosis and treatment initiation.

Results: Thyroid tissue stiffness was higher in SAT at baseline (214.26 ± 32.5 kPa) in comparison with values recorded at a 4-week follow-up (45.92 ± 17.4 kPa) and at 10 weeks following diagnosis and treatment initiation (21.65 ± 5.3 kPa, \( P < 0.0001 \)). Baseline thyroid stiffness in SAT was higher than that found in CAT (36.15 ± 18.7 kPa, \( P < 0.0001 \)) and CS (16.18 ± 5.4 kPa, \( P < 0.0001 \)). In the remission of SAT, thyroid stiffness was lower than that found in CAT (\( P = 0.006 \)), while it was higher than that in CS (\( P = 0.0008 \)). No difference was observed between thyroid stiffness in SAT at 4-week follow-up and in CAT. Patients with CAT presented higher thyroid stiffness than CS (\( P < 0.0001 \)), which was not influenced by L-thyroxine treatment. Thyroid stiffness in patients with AT was 216.6 and 241.9 kPa at baseline; after treatment, it decreased to 17.93 and 85.348 kPa respectively.

Conclusions: Sonoelastography may assist in the diagnosis and treatment monitoring of AT, SAT and CAT, as well as in the differentiation of the various types of thyroiditis.

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Introduction

Traditionally, palpation has been a part of a routine clinical evaluation of the thyroid, the aim of which is to examine tissue firmness. However, this method is highly subjective, and its interpretation varies depending on the size and location of the lesions, as well as the experience of the physician. Sonoelastography, sometimes referred to as ‘electronic palpation’, is a novel imaging technique used for the noninvasive and objective reconstruction of tissue stiffness, which measures the degree of its deformation in response to the application of an external force (1). It is based on the principle that abnormal tissue, affected with fibrosis, inflammatory infiltration or neoplastic process, tends to be stiffer than healthy tissue. The possibility of implementing this method in commercial ultrasound (US) systems and using it during routine US examinations is one of its great advantages. Although available from 1990, it was first used in thyroid examination in 2005 by Lyshchik et al. (2). Usefulness of the method in differentiating benign and malignant thyroid tumors has been widely described (3). Nevertheless, there is still no clear conclusion about its true clinical utility (2, 3, 4). However, the sonoelastographic image of thyroid inflammatory diseases has only occasionally been the subject of investigation.

Although acute thyroiditis (AT), subacute thyroiditis (SAT), and chronic autoimmune thyroiditis (CAT) have dissimilar origin and require different management, these conditions may share some parallel clinical, biochemical, and sonographic features, which might lead to confusion and, as a result, diagnostic difficulties. On the other hand, thyroid sonoelastography was found to be exceptionally useful in the evaluation of thyroid nodules; nevertheless, it remains unknown whether the
implementation of this method might bring further insight into the evaluation of thyroiditis. It is also uncertain whether a coexisting thyroid inflammation might influence the result of sonoelastographic evaluation of thyroid focal lesions. Thus, the aim of this study was to prospectively assess the sonoelastographic images of AT, SAT, and CAT at baseline and during remission, as well as to evaluate the applicability of sonoelastography in the diagnosis, differentiation, and treatment monitoring of the various types of thyroiditis.

Subjects and methods

Subjects

The studied group consisted of two patients with AT, 18 patients with granulomatous SAT, 18 patients with CAT and a group of 40 control subjects (CS) without thyroid pathology referred to the department for other conditions, matched for age and gender.

The patients underwent clinical examinations, routine blood tests, conventional US, followed by fine-needle aspiration biopsy (FNAB) if indicated, and a sonoelastographic examination. AT was diagnosed on the basis of clinical symptoms, including fever and painful goiter, accompanied by local lymphadenopathy, as well as the results of conventional US and cytological examination of the specimen obtained during FNAB. SAT was diagnosed in the presence of painful goiter, accompanied by an elevated erythrocyte sedimentation rate (ESR), moderately increased body temperature, decreased radioisotope uptake on the thyroid scintiscan, and a typical image acquired using conventional US. The latter involved an increase in the volume of the thyroid gland, especially in depth; it was accompanied by ill-defined regions of the thyroid parenchyma, characterized by areas of heterogeneous and decreased echogenicity, smoothly turning into those of normal echogenicity. To the group with CAT patients presenting hypothyroidism, elevated antithyroid autoantibodies and a diffusely decreased echogenicity of the thyroid parenchyma on conventional US were included. Subjects clinically and biochemically euthyroid, with a negative history of thyroid disease, and presenting no thyroid pathology on conventional US were included. Sub- jects clinically and biochemically euthyroid, with a negative history of thyroid disease, and presenting no thyroid pathology on conventional thyroid US were classified as CS.

The protocol of the study was accepted by the local ethics committee, and all the participants gave informed consent to participate.

Serum assays

ESR after 1 h was calculated by a classical method, while concentration of C-reactive protein (CRP) was assessed by a highly sensitive particle-enhanced immunoturbidimetric method. Assessment of hormone concentration was performed using Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics) and included measurement of serum TSH, free triiodothyronine (FT₃), and free thyroxine (FT₄). Thyroid autoantibody concentrations (TSH receptor antibody, TRAb; antithyroid peroxidase antibody, TPOAb; and antithyroglobulin antibody, TgAb) were assessed by radioimmunological method using commercially available BRAMHS anti-TPO, anti-Tg, and TRAK RIA kits and scintillation gamma counter (LKB Wallac CliniGamma 1272).

Thyroid imaging

At baseline, all the patients underwent conventional US and sonoelastographic evaluation using an AIXPLORER system by Supersonic Imagine, with the use of Shear Wave Elastography. All the examinations were performed by two experienced thyroid sonographers (M. R. and E. S.) and the obtained results were averaged. The stiffness of thyroid parenchyma was assessed in both a qualitative and a quantitative manner. By measuring the propagation velocity of the shear waves at every point of the image, an elasticity map could be deduced. This included color-coded displays depicting tissue stiffness using a color scale from blue (soft) through green and yellow (medium elasticity) to red (hard). The classification of the affected thyroid parenchyma in a 4-point modified Ueno scale was used to describe tissue stiffness, where elasticity score (ES) I meant completely normal thyroid elasticity (blue color); ES II, parenchyma of predominantly normal elasticity, however, containing areas of slightly increased stiffness (green and yellow color); ES III, parenchyma of intermediate elasticity, where yellow color predominates and may contain some tiny areas of highly increased stiffness, depicted in red; and ES IV, most of the thyroid parenchyma presents highly increased stiffness, with predominating red color (5). The classical 5-point Ueno elasticity scale was modified, as regions affected with thyroid inflammation presenting no clear margins were evaluated. The quantitative information was depicted as a stiffness index and expressed in kilopascals on a continuous scale. Tissue stiffness was quantified by Young’s Module E corresponding to the speed of propagation of the shear wave. As the method gives a possibility to evaluate stiffness at each point of interest, the stiffest area of a lesion was chosen for quantitative assessment of parenchymal firmness.

Cytological examination

US-guided FNAB of some detected lesions was performed to confirm the diagnosis and exclude thyroid malignancy. The cytological evaluation of the obtained specimens was performed by the two pathologists as a routine medical procedure in the Department of Pathology at Poznan University of Medical Sciences.
Interventions

Patients diagnosed with AT were given a course of wide-spectrum antibiotics (third-generation cephalosporin) intravenously. All subjects diagnosed with SAT underwent an 8-week anti-inflammatory treatment with gradually decreasing doses of prednisone (from 40 to 5 mg/day). Adjuvant treatment included 20 mg omeprazole and supplementation with potassium chloride. In subjects diagnosed with CAT, L-T4 substitution was introduced to restore euthyroidism. All the patients underwent prospective observation, with sonographic and sonoelastographic assessment during a 4-week follow-up visit and at 10 weeks following diagnosis and treatment initiation.

Statistical analysis

First, the relevant parameters were compared at baseline, during a 4-week follow-up, and at 10 weeks following diagnosis and treatment initiation for both the SAT and CAT patients using a nonparametric Friedman test; subsequently, a multiple comparison analysis was carried out with the post hoc Dunn test. Next, the results were confirmed with the Quade test, due to the extremely low P values. The exact P value was estimated on the basis of permutational techniques using STATXACT-9 statistical software (Cytel Software Corporation, Cambridge, MA, USA).

Comparisons between patients with SAT and subjects diagnosed with CAT and CS were performed with the nonparametric Mann–Whitney U test. As mentioned earlier, the exact P values confirmed the decisions based on the standard asymptotical P values. Patients with AT could not be involved in the statistical evaluation, since this group included very few subjects.

Results

The age and gender structure of the analyzed subgroups was as follows:

– patients diagnosed with AT – two women, aged 40 and 52 years
– patients diagnosed with SAT – 16 women and two men, aged 27–74 (median 49.5) years
– patients diagnosed with CAT – 16 women and two men, aged 25–71 (median 48) years
– CS – 36 women and four men, aged 21–78 (median 47.5) years.

FNAB was performed in 18 patients to confirm the diagnosis. In 13 of them, cytological diagnosis was consistent with SAT, in two with AT, and three biopsies were nondiagnostic. In the latter, SAT was diagnosed on the basis of clinical, laboratory, and sonoelastographic data. Patients with CAT were diagnosed on the basis of clinical and laboratory data, and sonoelastographic image; hence, they were not subject to FNAB.

A significant difference in thyroid tissue stiffness (qualitatively expressed on a 4-point scale, as well as quantitatively through the estimation of Young’s Module E) was noted between SAT at baseline (214.26 ± 32.5 kPa) in comparison with values recorded at a 4-week follow-up visit (45.92 ± 17.4 kPa) and at 10 weeks following diagnosis and treatment initiation (21.65 ± 5.3 kPa). Changes of the elastic properties of thyroid parenchyma were accompanied by a gradual normalization of biochemical parameters. The results of thyroid tissue stiffness and biochemical assessment of the patients, at the three phases of SAT, are presented in Table 1, together with the level of statistical significance. The stiffness of the thyroid parenchyma in SAT at baseline was additionally significantly higher when compared with that found in CAT (36.15 ± 18.7 kPa) or CS (16.18 ± 5.4 kPa), and with treatment was gradually restored to values close to normal (Fig. 1). Representative sonoelastographic images taken in SAT at baseline and during the recovery phase are presented in Fig. 2. The differences between thyroid tissue elasticity in the three phases of SAT, CAT and CS, assessed quantitatively as Young’s Module E, are presented in Table 2. Table 3 presents thyroid tissue stiffness evaluated qualitatively on a 4-point scale, where I indicates the lowest stiffness and IV indicates the highest. At the 4-week follow-up, no significant difference was observed between thyroid tissue stiffness in SAT (45.92 ± 17.4 kPa) and CAT (36.15 ± 18.7 kPa). However, during remission, after

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SAT (baseline) (1)</th>
<th>SAT (4-week follow-up) (2)</th>
<th>SAT (10-week follow-up) (3)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young’s Module E (kPa)</td>
<td>214.26 ± 32.5</td>
<td>45.92 ± 17.4</td>
<td>21.65 ± 5.3</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>62.6 ± 25.0</td>
<td>16.2 ± 7.9</td>
<td>7.1 ± 3.7</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>71.7 ± 71.9</td>
<td>10.2 ± 12.9</td>
<td>1.6 ± 1.8</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>TSH (mIU/ml)</td>
<td>0.091 ± 0.187</td>
<td>3.864 ± 3.950</td>
<td>2.059 ± 0.702</td>
<td>(1) vs (2) P &lt; 0.0001 (1) vs (3) P = 0.0392 (2) vs (3) NS</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>30.38 ± 12.47</td>
<td>14.53 ± 2.88</td>
<td>15.28 ± 2.09</td>
<td>(1) vs (2) P &lt; 0.0001 (1) vs (3) P = 0.006 (2) vs (3) NS</td>
</tr>
</tbody>
</table>

SAT, subacute thyroiditis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FT4, free thyroxine; NS, statistically nonsignificant.
treatment, patients with SAT presented significantly lower thyroid stiffness (21.65 ± 5.3 kPa) than that found in CAT (36.15 ± 18.7 kPa), while it was still higher in comparison with healthy CS (16.18 ± 5.4 kPa). Patients with CAT presented significantly higher thyroid stiffness in comparison with CS and thyroid elasticity was not influenced by L-T4 treatment.

Thyroid stiffness at baseline in the two women with AT was equal to 216.6 and 241.9 kPa (IV) respectively, while during remission, after the evacuation of pus and with antibacterial treatment, it decreased to 17.93 kPa (I) and 85.348 kPa (II) respectively (Fig. 3). Moreover, in subjects with AT or SAT, the region of the thyroid presenting increased stiffness in the sonoelastographic examination corresponded directly to the area most painful on palpation.

**Discussion**

Sonoelastography combines the advantages of high-frequency US and the possibility to assess the lesion’s stiffness (2). This novel sonographic technique is based on the difference in the viscoelastic properties between normal and pathological thyroid tissue, which corresponds to the tissue architecture. To date, sonoelastography has been mainly applied in the diagnostics of thyroid nodular disease (3). However, very little is known about the sonoelastographic image of inflammatory thyroid diseases.

A rare thyroid pathology clinically associated with an increased thyroid consistency is Riedel’s thyroiditis (6). The sonoelastographic image of Riedel’s thyroiditis in two patients has just been described, revealing heterogeneous stiffness of thyroid parenchyma ranging from 21 to 281 kPa (7). Thyroid tissue stiffness was found to be significantly higher in Graves’ disease, as well as in Hashimoto’s thyroiditis, when compared with healthy controls (8). Recently, our team has described the sonoelastographic image of two patients with SAT, characterized by significantly increased thyroid stiffness at baseline, which restored to values close to normal with remission (9). However, a literature search reveals no reports on sonoelastographic examination in AT.

AT usually presents with signs of both local and systemic inflammation. The patient may have fever up to 38–40 °C with malaise. On palpation, the thyroid may appear enlarged and tender, with pain radiating to...
Table 2 Thyroid tissue stiffness expressed in Young’s Module E (kPa) in the three phases of SAT, compared with CAT and CS.

<table>
<thead>
<tr>
<th>Young’s Module E (kPa)</th>
<th>SAT (baseline)</th>
<th>4-week follow-up</th>
<th>10-week follow-up</th>
<th>CAT baseline</th>
<th>CS baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT</td>
<td>(214.26 ± 32.5)</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>4-week follow-up (45.92 ± 17.4)</td>
<td>X</td>
<td>P &lt; 0.0001</td>
<td>X</td>
<td>NS</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>10-week follow-up (21.65 ± 5.3)</td>
<td>P &lt; 0.0001</td>
<td>X</td>
<td>P &lt; 0.0001</td>
<td>X</td>
<td>P &lt; 0.0008</td>
</tr>
<tr>
<td>CAT</td>
<td>(36.15 ± 18.7)</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
<td>P &lt; 0.0006</td>
<td>X</td>
</tr>
<tr>
<td>CS</td>
<td>(16.18 ± 5.4)</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0008</td>
<td>P &lt; 0.0001</td>
<td>X</td>
</tr>
</tbody>
</table>

SAT, subacute thyroiditis; CAT, chronic autoimmune thyroiditis; CS, control subjects.

Table 3 Thyroid tissue stiffness assessed qualitatively in a 4-point scale and the number of patients classified into the four groups.

<table>
<thead>
<tr>
<th>Thyroid stiffness</th>
<th>SAT (baseline)</th>
<th>SAT (4-week follow-up)</th>
<th>SAT (10-week follow-up)</th>
<th>CAT</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>–</td>
<td>4 (22.2%)</td>
<td>15 (83.3%)</td>
<td>6 (33.3%)</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>II</td>
<td>–</td>
<td>13 (72.2%)</td>
<td>3 (16.7%)</td>
<td>12 (66.7%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>III</td>
<td>1 (5.6%)</td>
<td>1 (5.6%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>17 (94.4%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SAT, subacute thyroiditis; CAT, chronic autoimmune thyroiditis; CS, control subjects.
in AT and SAT. On the other hand, thyroid stiffness in CAT was not significantly influenced by the introduction of $\text{L-T}_4$ treatment. The results of thyroid stiffness in our group of patients with CAT are comparable to those obtained in the study by Magri \textit{et al.} (18), though a little higher. A slight discordance might be attributed to the different number of subjects included in these studies. Another important issue is that all patients diagnosed with CAT in our study were on $\text{L-T}_4$ replacement therapy, while less than half of the patients enrolled in the study by Magri \textit{et al.} (18) needed $\text{L-T}_4$. The mean value of elasticity in this subgroup of 14 patients was noted to be higher than that in patients with no thyroid dysfunction. Since the lymphocytic infiltration and fibrosis are connected with the extent of thyroid parenchymal changes and functional impairment, it may be assumed that the elasticity values in CAT may correlate with these two histological features. Moreover, thyroid stiffness in the recovery phase of SAT and in CAT was found to be very similar, which, during this phase, makes arriving at a differential diagnosis on the basis of sonoelastography quite difficult. What is worth mentioning is that the degree of tissue stiffness and localization of the regions characterized by disturbed elasticity in SAT corresponded with the localization and intensity of pain reported by the patients.

The dissimilarities of thyroid stiffness observed in the three types of thyroiditis may be attributed to the differences in histopathologic architecture (19). The cytological specimen in AT is mostly composed of neutrophils and amorphous components of pus. On the other hand, an early phase of SAT is characterized by the disruption of follicles and neutrophil infiltration, with subsequent aggregation of lymphocytes, histiocytes and plasma cells. Multinucleated giant cells are quite typical; however, polymorphonuclear and lymphocytic populations may also be present (20, 21). Consequently, the areas of injury are replaced by a chronic inflammatory infiltrate and fibrosis (21). CAT is characterized mainly by focal or diffuse infiltrate of small mononuclear lymphocytes and Hürthle cell changes (12). Nevertheless, there is a wide overlap in cytomorphological features of thyroiditis, and therefore cytological analysis may not alone be used to determine diagnosis (20).

Another important issue is the fact that changes in thyroid firmness induced by thyroiditis may affect the evaluation of stiffness of thyroid focal lesions. Some authors reported that the coexistence of Hashimoto’s thyroiditis does not significantly influence the interpretation of the sonoelastographic image of concomitant thyroid nodules (1, 18, 22). However, it is still to be evaluated whether other types of thyroiditis might influence the result of thyroid nodules’ elasticity estimation. It is probable that SAT or AT, causing much more significant changes in elastic properties of the thyroid parenchyma than CAT, might importantly affect the estimated nodule firmness. As cases of coexistence of SAT with nodular goiter or thyroid cancer have been described, it seems best to postpone the assessment of the nodule stiffness until a complete recovery from SAT or AT (23).

In our study, the stiffness of thyroid parenchyma was assessed in both a qualitative and a quantitative manner and the obtained results were comparable. Recently, Park \textit{et al.} (24) demonstrated a high interobserver variability of the qualitative methods of elastographic evaluation, where the elasticity image and score depended on the extent of tissue compression. On the other hand, since the technique of Shear Wave Elastography used in our study is devoid of the need for freehand external compression, it can be assumed to be

\begin{figure}
\centering
\includegraphics[width=\textwidth]{thyroid_stiffness.png}
\caption{Thyroid stiffness in acute thyroiditis assessed (A) at baseline and (B) during remission after treatment.}
\end{figure}
operator independent, reproducible, and objective in the evaluation of tissue firmness (25).

The practical applicability of sonoelastography in thyroiditis might be limited, as several other clinical and laboratory tests coupled with conventional US usually provide a clinician with sufficient information to establish a diagnosis and decide on the management. Though palpation allows one to roughly assess the degree of thyroid firmness, elastographic imaging offers the quantitative and objective assessment of thyroid stiffness, an opportunity to follow changes in time, and the possibility to visualize the firmness of the dorsal parts of the thyroid. What is more, the examination is easy to perform and requires no more than 3–5 min in addition to the routinely performed conventional US (26).

Evidently, the changes of thyroid tissue stiffness observed in different types of thyroiditis are not specific and may not serve as the only factor determining the diagnosis. In addition to other factors, sonoelastography may be regarded as an adjunctive method supporting the diagnosis of thyroiditis, especially in cases of the so-called ‘gray zone’. Furthermore, it allows physicians to monitor the recovery of patients from AT or SAT, and thus influences the titration of medications. It is interesting to note that elasticity in convalescents from SAT is still significantly higher than that in controls. However, it might be attributed to the relatively short observation period in our study. It is also possible that the elasticity would become completely normal over the time of 10 weeks or more. Additionally, the lack of complete restoration of normal thyroid stiffness might indicate the coexistence of CAT. Further studies on larger groups of patients are required to confirm whether persistently increased thyroid stiffness in the recovery phase of SAT might be indicative of long-term hypothyroidism or disease recurrence.

There were some important limitations in this study, which should be mentioned. First, the number of enrolled patients was relatively small. Secondly, the main objective of this research was to show general differences between sonoelastographic images of various types of thyroiditis. Hence, detailed description of sonoelastographic image variation and its correlation with biochemical and cytological findings for each of the particular conditions was not included. However, that could be an interesting idea for further exploration on a larger group of patients.

In conclusion, AT and SAT are associated with an increased stiffness of the thyroid parenchyma, which is restored with treatment to values close to normal. CAT is associated with only a minimal increase in the stiffness of thyroid tissue, which remains unchanged during therapy. Sonoelastography may assist in the diagnosis and treatment monitoring of AT, SAT and CAT, as well as in the differentiation of the various types of thyroiditis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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